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DATE: Friday, December 08, 2006

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L8          16 L2 OR L3 OR L4 OR L5 OR L7

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L8   ANSWER 1 OF 16  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2005:1134223  CAPLUS
DN   144:396
TI   A novel small molecule CFTR inhibitor attenuates HCO3- secretion and
     duodenal ulcer formation in rats
AU   Akiba, Yasutada; Jung, Michael; Ouk, Samedy; Kaunitz, Jonathan D.
CS   Department of Medicine, School of Medicine, University of California, Los
     Angeles, CA, USA
SO   American Journal of Physiology (2005), 289(4, Pt. 1), G753-G759
     CODEN: AJPHAP; ISSN: 0002-9513
PB   American Physiological Society
DT   Journal
LA   English
AB   The cystic fibrosis (CF) transmembrane conductance regulator (CFTR) plays
     a crucial role in mediating duodenal bicarbonate (HCO3-) secretion (DBS).
     Although impaired DBS is observed in CF mutant mice and in CF patients, which
     would predict increased ulcer susceptibility, duodenal injury is rarely
     observed in CF patients and is reduced in CF mutant mice.  To explain this
     apparent paradox, we hypothesized that CFTR dysfunction increases cellular
     [HCO3-] and buffering power.  To further test this hypothesis, we examined
     the effect of a novel, potent, and highly selective CFTR inhibitor,
     CFTRinh-172, on DBS and duodenal ulceration in rats.  DBS was measured in
     situ using a standard loop perfusion model with a pH stat under isoflurane
     anesthesia.  Duodenal ulcers were induced in rats by cysteamine with or
     without CFTRinh-172 pretreatment 1 h before cysteamine.  Superfusion of
     CFTRinh-172 (0.1-10 μM) over the duodenal mucosa had no effect on basal
     DBS but at 10 μM inhibited acid-induced DBS, suggesting that its effect
     was limited to CFTR activation.  Acid-induced DBS was abolished at 1 and 3
     h and was reduced 24 h after treatment with CFTRinh-172, although basal
     DBS was increased at 24 h.  CFTRinh-172 treatment had no effect on gastric
     acid or HCO3- secretion.  Duodenal ulcers were observed 24 h after cysteamine
     treatment but were reduced in CFTRinh-172-pretreated rats.  CFTRinh-172
     acutely produces CFTR dysfunction in rodents for up to 24 h.  CFTR
     inhibition reduces acid-induced DBS but also prevents duodenal ulcer
     formation, supporting our hypothesis that intracellular HCO3- may be an
     important protective mechanism for duodenal epithelial cells.
RE.CNT  52    THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD
              ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT   307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-
     carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
     RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL
     (Biological study); USES (Uses)
        (CFTRh-172; novel small mol. CFTR inhibitor attenuates bicarbonate
        secretion and duodenal ulcer formation in rats)

L8   ANSWER 2 OF 16  CAPLUS  COPYRIGHT 2006 ACS on STN
AN   2005:108287  CAPLUS
DN   143:191261
TI   Predominant constitutive CFTR conductance in small airways
AU   Wang, Xiaofei; Lytle, Christian; Quinton, Paul M.
CS   Dept. Prediatrics, Med. Sch., Univ. California, San Diego, San Diego, CA,
     USA
SO   Respiratory Research (2005), 6(1), No pp. given
     CODEN: RREEBZ; ISSN: 1465-993X
     URL: http://respiratory-research.com/content/pdf/1465-9921-6-7.pdf
PB   BioMed Central Ltd.
DT   Journal; (online computer file)
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LA English
AB Background: The pathol. hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema). These forms of disease arise from chronic prolonged infections, which are usually never present in the normal lung. Despite the fact that primary hygiene and defense of the airways presumably requires a well controlled fluid environment on the surface of the bronchiolar airway, very little is know of the fluid and electrolyte transport properties of airways of less than a few mm diameter Methods: We introduce a novel approach to examine some of these properties in a preparation of minimally traumatized porcine bronchioles of about 1 mm diameter by microperfusing the intact bronchiole. Results: In bilateral isotonic NaCl Ringer solns., the spontaneous transepithelial potential (TEP; lumen to bath) of the bronchiole was small (mean+sem: -3± mV; n=25), but when gluconate replaced luminal Cl- the bionic Cl- diffusion potentials (-58±3 mV; n=25) were as large as -90 mV. TEP diffusion potentials from 2:1 NaCl dilution showed that epithelial Cl- permeability was at least 5 times greater than Na+ permeability. The anion selectivity sequence was similar to that of CFTR. The bionic TEP became more electroneg. with stimulation by luminal forskolin (5 μM)+IBMX (100 μM), ATP (100 μM), or adenosine (100 μM), but not by ionomycin. The TEP was partially inhibited by NPPB (100 μM), GlyH-101* (5-50 μM), and CFTRInh-172* (5 μM). RT-PCR gave identifying products for CFTR, α-, β-, and γ-ENaC and NKCC1. Antibodies to CFTR localized specifically to the epithelial cells lining the lumen of the small airways. Conclusion: These results indicate that the small airway of the pig is characterized by a constitutively active Cl- conductance that is most likely due to CFTR.
RE.CNT 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 307510-92-5
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anion conductance inhibitor CFTRInh-172 significantly depolarized transepithelial potential in pig bronchiole)

L8 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2005:37884 CAPLUS
DN 142:403893
TI In vivo pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents
AU Sonawane, N. D.; Muanprasat, Chatchai; Nagatani, Ray, Jr.; Song, Yuanlin; Verkman, A. S.
CS Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA
SO Journal of Pharmaceutical Sciences (2005), 94(1), 134-143
CODEN: JPMSAE; ISSN: 0022-3549
PB Wiley-Liss, Inc.
DT Journal
LA English
AB A small-mol. inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR), 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172), reduces enterotoxin-induced intestinal fluid secretion in rodents. Here, we study CFTRinh-172 pharmacol. and antidiarrheal efficacy in rodents using 14C-labeled CFTRinh-172, liquid chromatog./mass spectrometry, and a closed intestinal loop model of fluid secretion. CFTRinh-172 was cleared primarily by renal glomerular filtration without chemical modification. CFTRinh-172 accumulated in liver within 5 min after i.v. infusion in mice, and was concentrated fivefold in bile over blood. At 30-240 min, CFTRinh-172 was found mainly in liver, intestine, and kidney, with little detectable in the brain, heart, skeletal muscle, or lung. Pharmacokinetic anal. in rats following i.v. bolus infusion showed a distribution volume of 770 mL with redistribution and elimination half-times of 0.14 h and 10.3 h, resp. CFTRinh-172 was stable in hepatic microsomes. Closed-loop studies in mice

indicated that a single i.p. injection of 20 μg CFTRinh-172 inhibited fluid accumulation at 6 h after cholera toxin by >90% in duodenum and jejunum, .apprx.60% in ileum and <10% in colon. No toxicity was seen after high-dose CFTRinh-172 administration (3 mg/kg/day in two daily doses) in mice over the first 6 wk of life. The metabolic stability, enterohepatic recirculation, slow renal elimination, and intestinal accumulation of CFTRinh-172 account for its efficacy as an antidiarrheal.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 307510-92-5
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vivo pharmacol. and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents)

L8 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:671764 CAPLUS
DN 141:222260
TI Effects of a new cystic fibrosis transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts
AU Wang, X. F.; Reddy, M. M.; Quinton, P. M.
CS Department of Pediatrics, University of California San Diego, La Jolla, CA, 92093-0831, USA
SO Experimental Physiology (2004), 89(4), 417-425
CODEN: EXPHEZ; ISSN: 0958-0670
PB Blackwell Publishing Ltd.
DT Journal
LA English
AB Effective and specific inhibition of the cystic fibrosis transmembrane conductance regulator (CFTR) Cl- channel in epithelia has long been needed to better understand the role of anion movements in fluid and electrolyte transport. Until now, available inhibitors have required high concns., usually in the millimolar or high micromolar range, to effect even an incomplete block of channel conductance. These inhibitors, including 5-nitro-2(3-phenylpropyl-amino)benzoate (NPPB), bumetamide, glibenclamide and DIDS, are also relatively non-specific. Recently a new anion channel inhibitor, a thiazolidinone derivative, termed CFTRInh-172 has been synthesized and introduced with apparently improved inhibitory properties as shown by effects on anion conductance expressed in cell lines and on secretion in vivo. Here, we assay the effect of this inhibitor on a purely salt absorbing native epithelial tissue, the freshly isolated microperfused human sweat duct, known for its inherently high expression of CFTR. We found that the inhibitor at a maximum dose limited by its aqueous solubility of 5 μm partially blocked CFTR when applied to either surface of the membrane; however, it may be somewhat more effective from the cytosolic side (.apprx.70% inhibition). It may also partially inhibit Na+ conductance. The inhibition was relatively slow, with a half time for maximum effect of about 3 min, and showed very slow reversibility. Results also suggest that CFTR Cl- conductance (GCl) was blocked in both apical and basal membranes. The inhibitor appears to exert some effect on Na+ transport as well.

RE.CNT 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(CFTRInh-172; effects of new cystic fibrosis transmembrane conductance regulator inhibitor on Cl- conductance in human sweat ducts)

L8 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:506016 CAPLUS
DN 141:236485
TI Synthesis and characterization of a small molecule CFTR chloride channel inhibitor

AU He, Cheng-yan; Zhang, Heng-jun; Su, Zhong-min; Zhou, Jin-song; Yang, Hong; Ma, Tong-hui
CS Membrane Channel Research Laboratory, Northeast Normal University, Changchun, 130024, Peop. Rep. China
SO Chemical Research in Chinese Universities (2004), 20(3), 334-337
CODEN: CRCUED; ISSN: 1005-9040
PB Higher Education Press
DT Journal
LA English
AB A thiazolidinone CFTR inhibitor (CFTRinh-172) was synthesized by a three-step procedure with trifluoromethylaniline as the starting material. The synthesized CFTR inhibitor was characterized structurally by 1H-NMR and functionally in a CFTR-expressing cell line FRT/hCFTR/EYFP-H148Q by both fluorescent and electrophysiol. methods. A large amount (100 g) of high-quality small mol. thiazolidinone CFTR chloride channel inhibitor, CFTRinh-172, can be produced with this simple three-step synthetic procedure. The structure of the final product 2-thioxo-3-(3-trifluoromethylphenyl)-5-[4-carboxyphenyl-methylene]-4-thiazolidinone was confirmed by 1H NMR. The overall yield was 58% with a purity over 99% as analyzed by HPLC. The synthesized CFTRinh-172 specifically inhibited CFTR chloride channel function in a cell-based fluorescence assay (Kd≈1.5 μmol/L) and in a Ussing chamber-based short-circuit current assay (Kd≈0.2 μmol/L), indicating better quality than that of the com. combinatorial compound The synthesized inhibitor is nontoxic to cultured cells at a high concentration and to mouse at a high dose. The synthetic procedure developed here can be used to produce a large amount of the high-quality CFTRinh-172 suitable for antidiarrheal studies and for creation of cystic fibrosis models in large animals. The procedure can be used to synthesize radiolabeled CFTRinh-172 for in vivo pharmacokinetics studies.
RE.CNT 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 307510-92-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and characterization of a small mol. CFTR chloride channel inhibitor)

L8 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:290483 CAPLUS
DN 140:315071
TI Thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of CFTR-mediated diseases and conditions
IN Verkman, Alan; Ma, Tonghui
PA The Regents of the University of California, USA
SO PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	WO 2004028480	A3	20040701		

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US 2004063695 A1 20040401 US 2002-262573 20020930
CA 2500498 AA 20040408 CA 2003-2500498 20030930
AU 2003277162 A1 20040419 AU 2003-277162 20030930
US 2004235800 A1 20041125 US 2003-676727 20030930
EP 1549321 A2 20050706 EP 2003-798805 20030930
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IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
BR 2003014943 A 20050802 BR 2003-14943 20030930
JP 2006503853 T2 20060202 JP 2004-540305 20030930
PRAI US 2002-262573 A 20020930
US 2002-509049P P 20020930
US 2003-480253P P 20030620
WO 2003-US31005 W 20030930
OS MARPAT 140:315071
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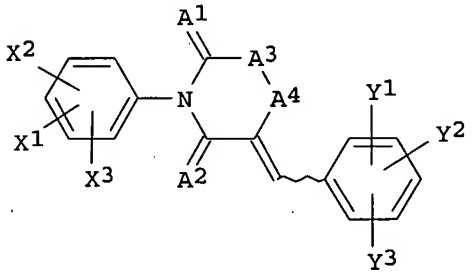

I

AB The invention discloses compns., pharmaceutical prepns. and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compns. and pharmaceutical prepns. of the invention may comprise one or more thiazolidinone compds. I (X1-X3, Y1-Y3=H, organic group, halo, nitro, azo, OH, mercapto; A1, A2=O, S; A3=S, Se; A4= ≥1 C or heteroatom or is absent), and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.

IT 307510-92-5P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of CFTR-mediated diseases and conditions)

IT 504-78-9D, Thiazolidine, derivs. 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 303056-54-4 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-

thioxo-4-thiazolidinone 535962-72-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone cystic fibrosis transmembrane conductance regulator protein inhibitors and pharmaceutical prepns. for treatment of CFTR-mediated diseases and conditions)

L8 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:269861 CAPLUS
DN 140:247127
TI Thiazolidinone compound cystic fibrosis transmembrane conductance regulator protein inhibitors, uses, and animal model of CFTR-mediated disease
IN Verkman, Alan; Ma, Tonghui
PA USA
SO U.S. Pat. Appl. Publ., 22 pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
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	WO 2004028480	A2	20040408	WO 2003-US31005	20030930
	WO 2004028480	A3	20040701		
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	EP 1549321	A2	20050706	EP 2003-798805	20030930
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
	BR 2003014943	A	20050802	BR 2003-14943	20030930
	CN 1684686	A	20051019	CN 2003-823366	20030930
	JP 2006503853	T2	20060202	JP 2004-540305	20030930
PRAI	US 2002-262573	A	20020930		
	US 2002-509049P	P	20020930		
	US 2003-480253P	P	20030620		
	WO 2003-US31005	W	20030930		

OS MARPAT 140:247127
AB The invention provides compns., pharmaceutical prepns., and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compns. and pharmaceutical prepns. of the invention may comprise one or more thiazolidinone compds., and may addnl. comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.
IT 141-84-4D, 2-Thioxo-4-thiazolidinone, derivs. 28600-65-9D,

Thiazolidinone, derivs. 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 303056-54-4 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
RL: BUU (Biological use, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)

L8 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2004:189841 CAPLUS
DN 141:254187
TI Prevention of toxin-induced intestinal ion and fluid secretion by a small-molecule CFTR inhibitor
AU Thiagarajah, Jay R.; Broadbent, Talmage; Hsieh, Emily; Verkman, Alan S.
CS Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, USA
SO Gastroenterology (2004), 126(2), 511-519
CODEN: GASTAB; ISSN: 0016-5085
PB W. B. Saunders Co.
DT Journal
LA English
AB Background & Aims: The cystic fibrosis transmembrane conductance regulator (CFTR) provides an important apical route for Cl- secretion across intestinal epithelia. A thiazolidinone-type CFTR blocker (CFTRinh-172) reduced cholera toxin-induced fluid accumulation in mouse intestinal loops. Here, we characterize the efficacy and pharmacodynamics of CFTRinh-172 in blocking cAMP and cGMP induced Cl-/fluid secretion in rodent and human intestine. Methods & Results: CFTRinh-172 inhibited cAMP and cGMP agonist induced short-circuit current by >95% in T84 colonic epithelial cells (KI .apprx. 3 μmol/L) and in mouse and human intestinal sheets (KI .apprx. 9 μmol/L). A single i.p. injection of CFTRinh-172 (200 μg) blocked intestinal fluid secretion in a rat closed-loop model by >90% for cholera toxin and >70% for STa Escherichia coli toxin. In mice, CFTRinh-172 (20 μg) inhibited cholera toxin-induced intestinal fluid secretion by 90% (persistence t1/2 .apprx.10 h, KI .apprx. 5 μg) and STa toxin by 75% (KI .apprx. 10 μg). Tissue distribution and pharmacokinetic studies indicated intestinal CFTRinh-172 accumulation facilitated by enterohepatic circulation. An oral CFTRinh-172 preparation reduced fluid secretion by >90% in a mouse open-loop cholera model. Conclusions: A small mol. CFTR blocker markedly reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxins. CFTR inhibition may thus reduce fluid secretion in infectious secretory diarrheas.
RE.CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 307510-92-5
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(thiazolidinone-type CFTR blocker CFTRinh-172 reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxin in rodent and human intestine without affecting intestinal fluid absorption)

L8 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2006 ACS on STN
AN 2002:932809 CAPLUS
DN 139:235
TI Thiazolidinone CFTR inhibitor identified by high-throughput screening

blocks cholera toxin-induced intestinal fluid secretion
AU Ma, Tonghui; Thiagarajah, Jay R.; Yang, Hong; Sonawane, Nitin D.; Folli, Chiara; Galietta, Luis J. V.; Verkman, A. S.
CS Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, 94143-0521, USA
SO Journal of Clinical Investigation (2002), 110(11), 1651-1658
CODEN: JCINAO; ISSN: 0021-9738
PB American Society for Clinical Investigation
DT Journal
LA English
AB Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults. The cystic fibrosis transmembrane conductance regulator (CFTR) protein is required for fluid secretion in the intestine and airways and, when defective, causes the lethal genetic disease cystic fibrosis. We screened 50,000 chemical diverse compds. for inhibition of cAMP/flavone-stimulated Cl- transport in epithelial cells expressing CFTR. Six CFTR inhibitors of the 2-thioxo-4-thiazolidinone chemical class were identified. The most potent compound discovered by screening of structural analogs, CFTRinh-172, reversibly inhibited CFTR short-circuit current in less than 2 min in a voltage-independent manner with K1 approx. 300 nM. CFTRinh-172 was nontoxic at high concns. in cell culture and mouse models. At concns. fully inhibiting CFTR, CFTRinh-172 did not prevent elevation of cellular cAMP or inhibit non-CFTR Cl- channels, multidrug resistance protein-1 (MDR-1), ATP-sensitive K+ channels, or a series of other transporters. A single i.p. injection of CFTRinh-172 (250 μg/kg) in mice reduced by more than 90% cholera toxin-induced fluid secretion in the small intestine over 6 h. Thiazolidinone CFTR inhibitors may be useful in developing large-animal models of cystic fibrosis and in reducing intestinal fluid loss in cholera and other secretory diarrheas.
RE.CNT 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT 141-84-4D, 2-Thioxo-4-thiazolidinone, derivs. 292174-08-4
301308-44-1 303056-54-4 307510-92-5
328250-71-1 535962-72-2
RL: PAC (Pharmacological activity); BIOL (Biological study)
(thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion)

L8 ANSWER 10 OF 16 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2005:231558 TOXCENTER
CP Copyright 2006 ACS
DN CA143111912610
TI Predominant constitutive CFTR conductance in small airways
AU Wang, Xiaofei; Lytle, Christian; Quinton, Paul M.
CS Dept. Prediatrics, Med. Sch., Univ. California, San Diego, San Diego, CA, USA.
SO Respiratory Research, (2005) Vol. 6, No. 1, pp. No pp. given.
CODEN: RREEBZ. ISSN: 1465-993X.
CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2005:108287
LA English
ED Entered STN: 30 Aug 2005
Last Updated on STN: 24 Jan 2006
AB Background: The pathol. hallmarks of chronic obstructive pulmonary disease (COPD) are inflammation of the small airways (bronchiolitis) and destruction of lung parenchyma (emphysema). These forms of disease arise from chronic prolonged infections, which are usually never present in the normal lung. Despite the fact that primary hygiene and defense of the airways presumably requires a well controlled fluid environment on the surface of the bronchiolar airway, very little is know of the fluid and electrolyte transport properties of airways of less than a few mm diameter

Methods: We introduce a novel approach to examine some of these properties in a preparation of minimally traumatized porcine bronchioles of about 1 mm diameter by microperfusing the intact bronchiole. Results: In bilateral isotonic NaCl Ringer solns., the spontaneous transepithelial potential (TEP; lumen to bath) of the bronchiole was small (mean+sem: -3± mV; n=25), but when gluconate replaced luminal Cl- the bionic Cl- diffusion potentials (-58±3 mV; n=25) were as large as -90 mV. TEP diffusion potentials from 2:1 NaCl dilution showed that epithelial Cl- permeability was at least 5 times greater than Na+ permeability. The anion selectivity sequence was similar to that of CFTR. The bionic TEP became more electroneg. with stimulation by luminal forskolin (5 μM)+IBMX (100 μM), ATP (100 μM), or adenosine (100 μM), but not by ionomycin. The TEP was partially inhibited by NPPB (100 μM), GlyH-101* (5-50 μM), and CFTRInh-172* (5 μM). RT-PCR gave identifying products for CFTR, α-, β-, and γ-ENaC and NKCC1. Antibodies to CFTR localized specifically to the epithelial cells lining the lumen of the small airways. Conclusion: These results indicate that the small airway of the pig is characterized by a constitutively active Cl- conductance that is most likely due to CFTR.

RN 28822-58-4 (IBMX)
58-61-7 (Adenosine)
56-65-5 (Adenosine tri-phosphate)
66575-29-9 (Forskolin)
2609-46-3 (Amiloride)
107254-86-4 (NPPB)
16887-00-6 (Chloride ion)
526-95-4 (D-Gluconic acid)
RN 307510-92-5; 328541-79-3

L8 ANSWER 11 OF 16 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2005:13450 TOXCENTER
CP Copyright 2006 ACS
DN CA14222403893D
TI In vivo pharmacology and antidiarrheal efficacy of a thiazolidinone CFTR inhibitor in rodents
AU Sonawane, N. D.; Muanprasat, Chatchai; Nagatani, Ray, Jr.; Song, Yuanlin; Verkman, A. S.
CS Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, 94143-0521, USA.
SO Journal of Pharmaceutical Sciences, (2005) Vol. 94, No. 1, pp. 134-143. CODEN: JPMSAE. ISSN: 0022-3549.
CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2005:37884
LA English
ED Entered STN: 18 Jan 2005
Last Updated on STN: 24 May 2005
AB A small-mol. inhibitor of the cystic fibrosis transmembrane conductance regulator (CFTR), 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone (CFTRinh-172), reduces enterotoxin-induced intestinal fluid secretion in rodents. Here, we study CFTRinh-172 pharmacol. and antidiarrheal efficacy in rodents using 14C-labeled CFTRinh-172, liquid chromatog./mass spectrometry, and a closed intestinal loop model of fluid secretion. CFTRinh-172 was cleared primarily by renal glomerular filtration without chemical modification. CFTRinh-172 accumulated in liver within 5 min after i.v. infusion in mice, and was concentrated fivefold in bile over blood. At 30-240 min, CFTRinh-172 was found mainly in liver, intestine, and kidney, with little detectable in the brain, heart, skeletal muscle, or lung. Pharmacokinetic anal. in rats following i.v. bolus infusion showed a distribution volume of 770 mL with redistribution and elimination half-times of 0.14 h and 10.3 h, resp. CFTRinh-172 was stable in hepatic microsomes. Closed-loop studies in mice indicated that a single i.p. injection of 20 μg CFTRinh-172 inhibited

fluid accumulation at 6 h after cholera toxin by >90% in duodenum and jejunum, .apprx.60% in ileum and <10% in colon. No toxicity was seen after high-dose CFTRinh-172 administration (3 mg/kg/day in two daily doses) in mice over the first 6 wk of life. The metabolic stability, enterohepatic recirculation, slow renal elimination, and intestinal accumulation of CFTRinh-172 account for its efficacy as an antidiarrheal.
RN 307510-92-5

L8 ANSWER 12 OF 16 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2004:144789 TOXCENTER
CP Copyright 2006 ACS
DN CA14115236485T
TI Synthesis and characterization of a small molecule CFTR chloride channel inhibitor
AU He, Cheng-yan; Zhang, Heng-jun; Su, Zhong-min; Zhou, Jin-song; Yang, Hong; Ma, Tong-hui
CS Membrane Channel Research Laboratory, Northeast Normal University, Changchun, 130024, Peop. Rep. China.
SO Chemical Research in Chinese Universities, (2004) Vol. 20, No. 3, pp. 334-337.
CODEN: CRCUED. ISSN: 1005-9040.
CY CHINA
DT Journal
FS CAPLUS
OS CAPLUS 2004:506016
LA English
ED Entered STN: 29 Jun 2004
Last Updated on STN: 29 Dec 2004
AB A thiazolidinone CFTR inhibitor (CFTRinh-172) was synthesized by a three-step procedure with trifluoromethylaniline as the starting material. The synthesized CFTR inhibitor was characterized structurally by 1H-NMR and functionally in a CFTR-expressing cell line FRT/hCFTR/EYFP-H148Q by both fluorescent and electrophysiol. methods. A large amount (100 g) of high-quality small mol. thiazolidinone CFTR chloride channel inhibitor, CFTRinh-172, can be produced with this simple three-step synthetic procedure. The structure of the final product 2-thioxo-3-(3-trifluoromethylphenyl)-5-[4-carboxyphenyl-methylene]-4-thiazolidinone was confirmed by 1H NMR. The overall yield was 58% with a purity over 99% as analyzed by HPLC. The synthesized CFTRinh-172 specifically inhibited CFTR chloride channel function in a cell-based fluorescence assay (Kd≈1.5 μmol/L) and in a Ussing chamber-based short-circuit current assay (Kd≈0.2 μmol/L), indicating better quality than that of the com. combinatorial compound The synthesized inhibitor is nontoxic to cultured cells at a high concentration and to mouse at a high dose. The synthetic procedure developed here can be used to produce a large amount of the high-quality CFTRinh-172 suitable for antidiarrheal studies and for creation of cystic fibrosis models in large animals. The procedure can be used to synthesize radiolabeled CFTRinh-172 for in vivo pharmacokinetics studies.
RN 98-16-8 (3-Trifluoromethylaniline)
619-66-9 (4-Carboxybenzaldehyde)
RN 307510-92-5; 315-08-2

L8 ANSWER 13 OF 16 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2004:60711 TOXCENTER
CP Copyright 2006 ACS
DN CA14116254187B
TI Prevention of toxin-induced intestinal ion and fluid secretion by a small-molecule CFTR inhibitor
AU Thiagarajah, Jay R.; Broadbent, Talmage; Hsieh, Emily; Verkman, Alan S.
CS Departments of Medicine and Physiology, Cardiovascular Research Institute, University of California, San Francisco, CA, USA.
SO Gastroenterology, (2004) Vol. 126, No. 2, pp. 511-519.
CODEN: GASTAB. ISSN: 0016-5085.

CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2004:189841
LA English
ED Entered STN: 16 Mar 2004
Last Updated on STN: 4 Jul 2006
AB Background & Aims: The cystic fibrosis transmembrane conductance regulator (CFTR) provides an important apical route for Cl- secretion across intestinal epithelia. A thiazolidinone-type CFTR blocker (CFTRinh-172) reduced cholera toxin-induced fluid accumulation in mouse intestinal loops. Here, we characterize the efficacy and pharmacodynamics of CFTRinh-172 in blocking cAMP and cGMP induced Cl-/fluid secretion in rodent and human intestine. Methods & Results: CFTRinh-172 inhibited cAMP and cGMP agonist induced short-circuit current by >95% in T84 colonic epithelial cells (KI .apprx. 3 μmol/L) and in mouse and human intestinal sheets (KI .apprx. 9 μmol/L). A single i.p. injection of CFTRinh-172 (200 μg) blocked intestinal fluid secretion in a rat closed-loop model by >90% for cholera toxin and >70% for STa Escherichia coli toxin. In mice, CFTRinh-172 (20 μg) inhibited cholera toxin-induced intestinal fluid secretion by 90% (persistence t1/2 .apprx.10 h, KI .apprx. 5 μg) and STa toxin by 75% (KI .apprx. 10 μg). Tissue distribution and pharmacokinetic studies indicated intestinal CFTRinh-172 accumulation facilitated by enterohepatic circulation. An oral CFTRinh-172 preparation reduced fluid secretion by >90% in a mouse open-loop cholera model. Conclusions: A small mol. CFTR blocker markedly reduced intestinal ion and fluid secretion caused by cAMP/cGMP-dependent bacterial enterotoxins. CFTR inhibition may thus reduce fluid secretion in infectious secretory diarrheas.
RN 7665-99-8 (Cyclic guanosine monophosphate)
RN 60-92-4; 307510-92-5

L8 ANSWER 14 OF 16 TOXCENTER COPYRIGHT 2006 ACS on STN
AN 2002:654803 TOXCENTER
CP Copyright 2006 ACS
DN CA13901000235U
TI Thiazolidinone CFTR inhibitor identified by high-throughput screening blocks cholera toxin-induced intestinal fluid secretion
AU Ma, Tonghui; Thiagarajah, Jay R.; Yang, Hong; Sonawane, Nitin D.; Folli, Chiara; Galietta, Luis J. V.; Verkman, A. S.
CS Department of Medicine, Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA, 94143-0521, USA.
SO Journal of Clinical Investigation, (2002) Vol. 110, No. 11, pp. 1651-1658. CODEN: JCINAO. ISSN: 0021-9738.
CY UNITED STATES
DT Journal
FS CAPLUS
OS CAPLUS 2002:932809
LA English
ED Entered STN: 18 Dec 2002
Last Updated on STN: 24 Nov 2003
AB Secretory diarrhea is the leading cause of infant death in developing countries and a major cause of morbidity in adults. The cystic fibrosis transmembrane conductance regulator (CFTR) protein is required for fluid secretion in the intestine and airways and, when defective, causes the lethal genetic disease cystic fibrosis. We screened 50,000 chemical diverse compds. for inhibition of cAMP/flavone-stimulated Cl- transport in epithelial cells expressing CFTR. Six CFTR inhibitors of the 2-thioxo-4-thiazolidinone chemical class were identified. The most potent compound discovered by screening of structural analogs, CFTRinh-172, reversibly inhibited CFTR short-circuit current in less than 2 min in a voltage-independent manner with K1 approx. 300 nM. CFTRinh-172 was nontoxic at high concns. in cell culture and mouse models. At concns. fully inhibiting CFTR, CFTRinh-172 did not prevent elevation of cellular

cAMP or inhibit non-CFTR Cl- channels, multidrug resistance protein-1 (MDR-1), ATP-sensitive K+ channels, or a series of other transporters. A single i.p. injection of CFTRinh-172 (250 μg/kg) in mice reduced by more than 90% cholera toxin-induced fluid secretion in the small intestine over 6 h. Thiazolidinone CFTR inhibitors may be useful in developing large-animal models of cystic fibrosis and in reducing intestinal fluid loss in cholera and other secretory diarrheas.

RN 141-84-4Q (2-Thioxo-4-thiazolidinone, derivs.)
16887-00-6 (Chloride)
RN 292174-08-4; 301308-44-1; 303056-54-4; 307510-92-5; 328250-71-1; 535962-72-2

L8 ANSWER 15 OF 16 USPATFULL on STN
AN 2004:299931 USPATFULL
TI Cystic fibrosis transmembrane conductance regulator protein inhibitors and uses thereof
IN Verkman, Alan, San Francisco, CA, UNITED STATES
Ma, Tonghui, San Francisco, CA, UNITED STATES
PI US 2004235800 A1 20041125
AI US 2003-676727 A1 20030930 (10)
PRAI US 2002-509049P 20020930 (60)
US 2003-480253P 20030620 (60)
DT Utility
FS APPLICATION
LREP BOZICEVIC, FIELD & FRANCIS LLP, 1900 UNIVERSITY AVE, SUITE 200, EAST PALO ALTO, CA, 94303
CLMN Number of Claims: 64
ECL Exemplary Claim: 1
DRWN 14 Drawing Page(s)
LN.CNT 2476
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides compositions, pharmaceutical preparations and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compositions and pharmaceutical preparations of the invention may comprise one or more thiazolidinone compounds, and may additionally comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound. In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound. In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 141-84-4D, 2-Thioxo-4-thiazolidinone, derivs. 28600-65-9D, Thiazolidinone, derivs. 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 303056-54-4 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)

L8 ANSWER 16 OF 16 USPATFULL on STN

AN 2004:83239 USPATFULL
TI Cystic fibrosis transmembrane conductance regulator protein inhibitors and uses thereof
IN Verkman, Alan, San Francisco, CA, UNITED STATES
Ma, Tonghui, San Francisco, CA, UNITED STATES
PI US 2004063695 A1 20040401
AI US 2002-262573 A1 20020930 (10)
DT Utility
FS APPLICATION
LREP BOZICEVIC, FIELD & FRANCIS LLP, 200 MIDDLEFIELD RD, SUITE 200, MENLO PARK, CA, 94025
CLMN Number of Claims: 62
ECL Exemplary Claim: 1
DRWN 5 Drawing Page(s)
LN.CNT 1526
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides compositions, pharmaceutical preparations and methods for inhibition of cystic fibrosis transmembrane conductance regulator protein (CFTR) that are useful for the study and treatment of CFTR-mediated diseases and conditions. The compositions and pharmaceutical preparations of the invention may comprise one or more thiazolidinone compounds, and may additionally comprise one or more pharmaceutically acceptable carriers, excipients and/or adjuvants. The methods of the invention comprise, in certain embodiments, administering to a patient suffering from a CFTR-mediated disease or condition, an efficacious amount of a thiazolidinone compound. In other embodiments the invention provides methods of inhibiting CFTR that comprise contacting cells in a subject with an effective amount of a thiazolidinone compound. In addition, the invention features a non-human animal model of CFTR-mediated disease which model is produced by administration of a thiazolidinone compound to a non-human animal in an amount sufficient to inhibit CFTR.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT 141-84-4D, 2-Thioxo-4-thiazolidinone, derivs. 28600-65-9D, Thiazolidinone, derivs. 292174-08-4, 3-[(3-Trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 301308-44-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone 303056-54-4 307510-92-5, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone 328250-71-1, 3-[(3-Trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone 535962-72-2, 3-[(3-Trifluoromethyl)phenyl]-5-[(4-carboxyoxyphenyl)methylene]-2-thioxo-4-thiazolidinone
(thiazolidinone compound CFTR inhibitors, uses, and animal model of CFTR-mediated disease)